Evidence-based Guideline: Evaluation, Diagnosis, and Management of Congenital Muscular Dystrophy

Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Issues Review Panel of the American Association of Neuromuscular & Electrodiagnostic Medicine

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ABBREVIATIONS

AAN: American Academy of Neurology

AANEM: American Association of Neuromuscular & Electrodiagnostic Medicine

B3GALNT2: β-1,3-N-acetylgalactosaminyltransferase 2

B3GNT1: β-1,3-N-acetylglucosaminyltransferase 1

CK: creatine kinase

CMD: congenital muscular dystrophy

CMDs: congenital muscular dystrophies

COL6A1: collagen 6α1

COL6A2: collagen 6α2

COL6A3: collagen 6α3

DAG1: α-dystroglycan

EVID: statements supported directly by the systematically reviewed evidence

FHL1: four-and-a-half LIM domain 1

FKRP: fukutin-related protein

FKTN: fukutin

FVC: forced vital capacity

GMPPB: GDP-mannose pyrophosphorylase B

INFER: An inference from one or more of the other statements

LAMA2: laminin α2

L-CMD: *LMNA*-associated CMD

LGMD: limb-girdle muscular dystrophy

LMNA: lamin A/C

MD: muscular dystrophy

MDCs: merosin-deficient CMDs

MDs: muscular dystrophies

POMGnT2/GTDC2: POMGnT2

PRIN: an accepted axiom or principle

RELA: statements supported by strong evidence not included in the systematic review

SD: standard deviation

SEPN1: selenoprotein 1

SGK196: protein-O-mannose kinase

TMEM5: TMEM5

ABSTRACT

Objective. To delineate optimal diagnostic and therapeutic approaches to congenital muscular dystrophy (CMD) through a systematic review and analysis of the currently available literature.

Methods. Relevant, peer-reviewed research articles were identified using a literature search of the MEDLINE, EMBASE, and Scopus databases. Diagnostic and therapeutic data from these articles were extracted and analyzed in accordance with the American Academy of Neurology classification of evidence schemes for diagnostic, prognostic, and therapeutic studies. Recommendations were linked to the strength of the evidence, other related literature, and general principles of care.

Results. The geographic and ethnic backgrounds, clinical features, brain imaging studies, muscle imaging studies, and muscle biopsies of children with suspected CMD help predict subtype-specific diagnoses. Genetic testing can confirm some subtype-specific diagnoses, but not all causative genes for CMD have been described. Seizures and respiratory complications occur in specific subtypes. There is insufficient evidence to determine the efficacy of various treatment interventions to optimize respiratory, orthopedic, and nutritional outcomes, and more data are needed with regard to complications.

Recommendations. Multidisciplinary care by experienced teams is important for diagnosing and promoting the health of children with CMD. Accurate assessment of clinical presentations and genetic data will help in identifying the correct subtype-specific diagnosis in many cases. Multiorgan system complications occur frequently; surveillance and prompt interventions are likely to be beneficial for affected children. More research is needed to fill gaps in knowledge with regard to this category of muscular dystrophies.

The congenital muscular dystrophies (CMDs) are a group of rare muscular dystrophies (MDs) that have traditionally been defined as having symptom onset at birth. CMDs are distinct from congenital myopathies, which are characterized by different pathological features and genetic etiologies.[e1] Epidemiologic data are sparse. The prevalence has been reported to be 6.8×10^{-6} in 1993 in northeast Italy[e2] and 2.5×10^{-5} among children aged 16 years and younger in western Sweden,[e3] data which suggest that at least in European populations, the prevalence is likely to be in the range of 1 in 100,000 people. The genetic origins of many cases of congenital muscular dystrophy (CMD) have been discovered,[e4] and genetic testing is now a valuable component of the diagnostic evaluation; however, many affected individuals remain without a genetic diagnosis, an indication that novel genes have yet to be identified. Clinical genetic testing through Sanger sequencing is available for virtually all genes known to be associated with CMD. Although the diagnosis remains essentially a clinical one, especially for the classical subtypes defined below, genetic discoveries have expanded the recognized phenotypic spectrum of these disorders, and precise genotype–phenotype correlations will become increasingly important in the future. A recently published set of algorithms will help with the diagnostic process for these patients.[e5]

Traditionally, symptoms of CMD were expected to be present at birth or soon thereafter, as the term suggests. However, owing in part to recent genetic advances, a broader phenotypic spectrum is now recognized for CMD,[e5] and the exact age at onset may be difficult to define in some cases, especially for the milder variants. One study found that the mean age at onset of symptoms for Ullrich CMD is 12 months, suggesting that many cases of certain subtypes may have onset of symptoms later than was previously thought.[e6] Thus, MDs with onset in the first 2 years of life, especially during infancy (the first year of life), are now commonly considered to be CMDs, although this expanded range raises the possibility of overlap in age at onset with other MDs such as limb-girdle muscular dystrophy (LGMD). One lingering nosological question is whether a later-onset disease that is allelic to a CMD should be classified as a CMD or a different disease. In the case of several dystroglycanopathy genes, most notably *FKRP*, the CMD and LGMD phenotypes were established before it was evident that the relevant subtypes of these 2 disease categories shared the same genetic etiologies. Thus, at present, the later-onset diseases are generally categorized differently, but this may change as characterization of all of these diseases improves.

Progressive skeletal muscle weakness and hypotonia are the cardinal clinical manifestations. Serum creatine kinase (CK) levels are typically but not invariably elevated. As with other MDs, the CMDs share characteristic muscle biopsy findings: necrosis, regenerating fibers, fiber size variability, and increased perimysial and endomysial connective tissue. In contrast with most other MDs, certain subcategories of CMDs are frequently associated with brain and eye malformations. The range of structural and functional CNS outcomes is broad in CMDs; many patients, especially those with dystroglycanopathies, often have severe brain abnormalities, whereas many others have completely intact cognition throughout their lives.

Three major categories of CMDs are commonly recognized, each of which has distinct, well-described phenotypic features: (1) collagenopathies (also known as collagen VI–related

myopathies), including Ullrich CMD and Bethlem myopathy[e7,e8]; (2) merosinopathies (also known as merosin-deficient CMDs [MDCs], laminin α2 [*LAMA2*]–related CMDs, and MDC1A); and (3) dystroglycanopathies (also known as α-dystroglycan-related MDs), including Fukuyama CMD,[e9] muscle–eye–brain disease, and Walker–Warburg syndrome. A broad spectrum of dystroglycanopathies exists that also includes rare variants such as fukutin-related protein (*FKRP*) and *LARGE*-associated CMDs, as well as mild phenotypes that fall within the phenotypic spectrum of LGMD. There are other rare CMDs that do not fit into any of the classic categories, including rigid spine muscular dystrophy (MD), which overlaps with multiminicore disease and has been associated with mutations in selenoprotein 1 (*SEPN1*) and four-and-a-half LIM domain 1 (*FHL1*),[e10,e11] lamin A/C (*LMNA*)–associated CMD (L-CMD),[e12] and diseases that share features of both CMD and congenital myopathy, such as early-onset myopathy, areflexia, respiratory distress, and dysphagia (caused by mutations in *MEGF10*).[e13–e15] Rigid spine syndrome associated with *FHL1* mutations may be associated with reducing bodies on muscle biopsy.[e11] Tables e-1 and e-2 list these CMDs with their associated genes and clinical phenotypes. More recently, several other genes have been associated with CMDs, including *GTDC2*,[e16] *TMEM5*,[e17] *B3GALNT2*,[e18] *SGK196*,[e19] *B3GNT1*,[e20] *GMPPB*,[e21] and *DAG1*.[e22]

CMDs are most often autosomal recessive, but some cases have been found to follow autosomal dominant patterns, by direct inheritance, spontaneous mutations, or mosaicism. Emery–Dreifuss MD is generally not classified as a CMD, and thus no X-linked forms of CMDs have been described to date. Suspected founder mutations have led to clusters of certain mutations in discrete populations, such as *POMGnT1* mutations causing muscle–eye–brain disease in Finland,[e23] *FKTN* mutations causing Fukuyama CMD in Japan,[e24] and *FKTN* mutations causing Walker–Warburg syndrome in the Ashkenazi Jewish community.[e25,e26] Other clusters are likely to be found in the future.

Whereas the genetic, pathophysiologic, and pathological features of the CMDs have become better understood in recent decades, optimal diagnostic and therapeutic approaches remain unclear. This evidence-based guideline reviews the literature on the evaluation, diagnosis, and management of patients with suspected CMD. Duchenne MD, LGMD, myotonic dystrophy, and facioscapulohumeral dystrophy are not included in this guideline, as they are or will be discussed in other guidelines (one published,[e27] the others forthcoming). We assessed the efficacy of various screening and diagnostic procedures and therapeutic interventions for the management of patients with suspected or definite CMD. The guideline seeks to answer the following clinical questions:

1. For children with suspected CMD, how accurately do the (a) geographic location and ethnicity, (b) clinical features, (c) brain imaging findings, (d) muscle imaging findings, and (e) muscle biopsy findings predict the subtype-specific diagnosis?
2. How often does genetic testing confirm a diagnosis of CMD?
3. How often do patients with CMD experience cognitive, respiratory, and cardiac complications?

4. Are there effective treatments for complications of CMD, including scoliosis and nutritional deficiencies?

Appendix e-1 provides a brief glossary of common terms related to genetics and genetic sequencing, and appendix e-2 lists resources for genetic testing.

DESCRIPTION OF THE ANALYTIC PROCESS

This guideline was developed in accordance with the processes outlined in the 2004 and 2011 American Academy of Neurology (AAN) process manuals.[e28,e29] In July 2010, the American Academy of Neurology (AAN) Guideline Development Subcommittee and the American Association of Neuromuscular & Electrodiagnostic Medicine Practice Issues Review Panel (appendices e-3 through e-5) formed a panel of pediatric neurologists, a pediatric physiatrist, a pediatric critical care specialist, a patient advocate who also is a physician, and an AAN evidence-based medicine methodologist, selected to represent a range of expertise in CMDs. The panel searched the MEDLINE, EMBASE, and Scopus databases for relevant, peer-reviewed articles in humans and in all languages (see appendix e-6 for full search strategy and terms). The initial search identified 2,008 abstracts. Of those, 811 articles were selected for full-text review. An updated search of Medline in June 2012 and EMBASE and Scopus in August 2012 yielded an additional 1,090 articles, 70 of which were selected for review. Two panel members working independently of each other reviewed each of the 881 selected articles. Seventy-eight articles were selected for inclusion in the final review. Two panel members rated each of those articles, using the 2011 AAN criteria for classification of therapeutic and screening articles (appendix e-7). Questions 1, 2, and 3 are screening questions, and question 4 is a therapeutic question. A third panel member arbitrated any differences in article ratings.

We included articles in the review if they pertained to any of the following conditions: CMD, Ullrich disease, Bethlem myopathy, merosin deficiency, Walker–Warburg syndrome, muscle–eye–brain disease, Fukuyama CMD. Case reports were excluded. Class I, II, and III studies are discussed in the text. To target the specific treatment questions listed previously, we limited the search methodology to the CNS, myocardial dysfunction/arrhythmias, and respiratory complications (e.g., recurrent infections from presumed aspiration, hypopnea, hypoxemia, restrictive/neuromuscular insufficient lung disease).

The panel formulated a rationale for recommendations based on the evidence systematically reviewed and stipulated axiomatic principles of care. We explain this rationale in a section which precedes each set of recommendations. From this rationale, we inferred corresponding actionable recommendations. We assigned a level of obligation to each recommendation using a modified Delphi process that considered the following prespecified domains: the confidence in the evidence systematically reviewed, the acceptability of axiomatic principles of care, the strength of indirect evidence, and the relative magnitude of benefit to harm. Additional factors explicitly considered by the panel that could modify the level of obligation include judgments regarding the importance of outcomes, cost of compliance to the recommendation relative to benefit, the availability of the intervention, and anticipated variations in patients' preferences. Appendix e-8 presents the prespecified rules for determining the final level of obligation from these domains. We indicated the level of obligation using standard modal operators. *Must* corresponds to *Level*

A, very strong recommendations; *should* to *Level B*, strong recommendations; and *might* to *Level C*, weak recommendations. Appendix e-9 indicates the panel members' judgments supporting the level of obligation for each recommendation.

ANALYSIS OF EVIDENCE

Question 1 focuses on clinical features, question 2 on genetic diagnosis, question 3 on complications, and question 4 on treatments. The literature review yielded significantly more articles relevant to diagnostic questions than to ones involving complications and therapeutic issues. Thus, for the purpose of analysis, we divided question 1 into 5 subquestions.

We found only a few large studies and a number of smaller studies, most likely because of the rareness of CMD and the fact that the available studies oftentimes focus on specific subtypes. The panel decided to include at least some smaller studies so as not to miss what likely would be a significant number of valuable data, and thus set a minimum sample size of only 2 unrelated families for inclusion and a minimum evidence level of Class III for either diagnostic or screening criteria. In the end, many of the smallest studies were excluded because they provided only low levels of evidence (Class IV); however, a small number of these studies contributed data that were not readily available in studies that were rated Class III or higher, and thus were included in the analysis.

Clinical features.

Question 1a. For children with suspected CMD, how accurately do the geographic location and ethnicity predict the subtype-specific diagnosis?

One Class I article, 4 Class II articles, and 1 Class III article were identified. In the Class I article, screening of the Japanese population with clinical Fukuyama CMD revealed that 87% carry the retrotransposal founder mutation in *FKTN*, with an additional 9 nonfounder compound heterozygous mutations identified, leading to the severe phenotype.[e30] Carrier frequency for the founder mutation in Japan is 6/676.[e24,e30] The Class III article found *FKTN* mutations in 9 of 12 patients with α-dystroglycanopathy in Korea.[e31] In the first Class II article, 4 Ashkenazi Jewish patients with Walker−Warburg syndrome were identified as having a founder mutation in *FKTN*, c.1167insA, with a carrier frequency of 2/299.[e26] The second Class II article reported that an A200P haplotype in the *POMT1* gene was found in 5 Turkish patients, all presenting with a similar clinical phenotype based on an early age at onset (1−3 years), age at onset of ambulation (3−4 years), the presence of calf and thigh hypertrophy, developmental disability (IQ 50−65), significant elevations in the serum CK level (> 20-fold over normal), and a lack of structural brain abnormalities on CT and MRI scans.[e32] The next 2 Class II studies found that *LAMA2* mutations were common in children with biopsy-confirmed merosin deficiency in Europe, North

Africa, and Korea (see Question 1e, discussed later[e33,e34]). Merosin deficiency has been reported to be a common subtype in several populations, including in Brazilians (see Question 1e[e35]).

Conclusion. In children with suspected CMD, founder mutations exist in the Japanese, Ashkenazi Jewish, and Turkish populations. Other founder mutations likely exist. Thus, the geographic and ethnic background of children with suspected CMD may help predict the specific subtype when published information is available for the population of interest (1 Class I study,[e30] 4 Class II studies,[e26,e32–e34] 1 Class III study[e31]).

Question 1b. For children with suspected CMD, do certain clinical features accurately predict the subtype-specific diagnosis?

Eight articles addressed this question: 1 Class II article and 1 Class III article for collagenopathies, 1 Class II article for merosinopathy, 1 Class II study and 3 Class III studies involving dystroglycanopathies, and 1 Class III study involving L-CMD.

Distal joint hyperlaxity is a characteristic clinical feature of collagenopathy. In the Class II study of collagenopathies, 4 patients were described with a congenital presentation of marked distal hyperlaxity and diaphragmatic paralysis. They were found to have homozygous or compound heterozygous mutations consistent with the diagnosis of Ullrich CMD.[e36] In the Class III study of collagenopathies, 3 patients shared common features: congenital hypotonia, joint contractures, high-arched palate, prominent calcaneus, scoliosis, hyperhidrosis, normal intelligence, and normal serum CK levels. EMG was myopathic. Muscle biopsy demonstrated variation in muscle fiber diameter with increased connective tissues. These patients were diagnosed with Ullrich CMD.[e37]

A hallmark of merosinopathy is a pattern of white matter abnormalities of the brain in conjunction with congenital weakness. In a third Class II article, 13 patients with merosin deficiency were found to have congenital weakness, elevated serum CK levels, and white matter signal abnormalities on brain MRI. The MRI findings did not include cortical malformations such as lissencephaly and pachygyria. These patients were found to have merosin deficiency on immunohistochemistry of their muscle biopsy tissue, and partial deficiency correlated with a milder phenotype than complete deficiency.[e38]

The dystroglycanopathies in their syndromic forms are typically characterized by muscle weakness, structural eye abnormalities, and cortical brain abnormalities, this last often associated with migrational defects. Fukuyama CMD tends to be milder in phenotype, and muscle–eye–brain disease is generally moderately severe. Walker–Warburg syndrome often carries the most severe structural and functional abnormalities as well as the shortest life expectancy. In the fourth Class II article, 31 of 92 patients (34%) with a suspected clinical diagnosis of dystroglycanopathy were found to have mutations in associated genes.[e39] The second Class III

article identified a cohort of 26 patients with clinical features of muscle–eye–brain disease who were found to have mutations in *POMGnT1*.[e40] The third Class III article found that patients with the clinical features of muscle–eye–brain disease tend to have necrotic and regenerative fibers on muscle biopsy during infancy, whereas fat infiltration becomes more prominent when the muscle biopsy is performed later in childhood. Secondary merosin deficiency was a common finding.[e41] In the fourth Class III article, patients with clinical features of Walker–Warburg syndrome, characterized by severe weakness at birth, accompanied by severe structural abnormalities in the brain and eyes, were found to have mutations in *POMT1*, a known causative gene.[e42]

The fifth Class III study examined the clinical features for various MD forms associated with *LMNA* mutations and found that L-CMD is strongly associated with neck extensor weakness.[e43]

Conclusion. In children with suspected CMD, clinical features may predict specific subtype diagnoses and may in some cases predict the causative genes (3 Class II[e36–e38] and 5 Class III articles[e39–e43]).

Question 1c. For children with suspected CMD, how accurately do the brain imaging findings predict the subtype-specific diagnosis?

Two Class II studies and 1 Class III study addressed this question. The first Class II study identified characteristic white matter abnormalities on brain MRI suggestive of a merosinopathy diagnosis and found that these imaging results correlated with merosin deficiency on muscle biopsy.[e44] In the second Class II study, two specific cerebellar abnormalities were found to be strongly correlated with the diagnosis of Fukuyama CMD: disorganized cerebellar folia (found in 16 of 25 cases) and intraparenchymal cysts (found in 23 of 25 cases).[e45] The Class III study examined 4 patients with dystroglycanopathy confirmed by clinical, histologic, and radiographic criteria and found that all 4 demonstrated polymicrogyria, white matter lesions, pontine hypoplasia, and subcortical cerebellar cysts.[e46]

Conclusion. Abnormal findings on brain imaging studies can predict the subtype-specific diagnosis in some cases, especially in merosinopathy and some dystroglycanopathies (2 Class II studies[e44,e45] and 1 Class III study[e46]).

Question 1d. For children with suspected CMD, how accurately does muscle imaging predict the subtype-specific diagnosis?

There were 3 Class I articles and 1 Class III article. In the first Class I article, children with suspected neuromuscular disease underwent qualitative muscle ultrasound. Ultrasound distinguished normal from diseased muscle with a sensitivity of 81% and specificity of 96%. A highly characteristic central shadow pattern for Bethlem myopathy, one of the collagenopathies,

was identified.[e47] In the second Class I article, ultrasound and EMG successfully aided in the classification of infants as those with neurogenic disorders, those with myopathic disorders, and those with no neuromuscular disorder.[e48] In the third Class I article, lower-extremity MRI showed specific patterns in patients with collagenopathy (34 of 40 patients) and *SEPN1*-related myopathy (12 of 13 patients) that indicated the subtype-specific diagnosis.[e49] The Class III study compared muscle CT findings of 14 patients with confirmed Ullrich CMD or Bethlem myopathy with the findings of 13 patients with confirmed Emery–Dreifuss MD, and found that CT muscle imaging could distinguish reliably between the 2 groups.[e50]

Conclusion. Skeletal muscle imaging in children with suspected CMD using MRI, ultrasound, and CT often demonstrates signal abnormalities that suggest subtype-specific diagnoses. This has been most extensively documented in CMD subtypes associated with rigidity of the spine, such as collagenopathies and *SEPN1*-related myopathy. These conclusions are based on 3 Class I articles[e47–e49] and 1 Class II article.[e50]

Question 1e. Do children with specific muscle biopsy findings have specific CMD subtypes?

Three Class II articles and 1 Class III article addressed this question for merosinopathy, 1 Class III article for laminopathies, and 1 Class III article for CMD in general. The 3 Class II articles found that merosin deficiency on muscle biopsy correlated strongly with mutations in *LAMA2* in a cohort originating primarily from Europe and North Africa,[e33] a Japanese cohort where 1 in 40 children was found to have merosinopathy,[e51] and a cohort of 35 Korean patients wherein 8 (23%) had merosinopathy.[e34] The Class III article involving merosin deficiency examined 46 patients with immunohistochemistry. This study found that merosin deficiency correlated strongly with genetic mutations in *LAMA2* and that the patients in whom merosin was absent were more likely to have a severe phenotype as compared with the ones with partial deficiency.[e52] The Class III article involving CMD in general studied a Brazilian cohort of 59 patients with suspected CMD and found that 32 had merosin-positive CMD, 23 had merosin-deficient CMD, 1 had Ullrich CMD, and 3 had Walker–Warburg syndrome. In this cohort, partial merosin deficiency did not predict a less severe phenotype than complete merosin deficiency. A deficiency of α-dystroglycan on muscle biopsy predicted a severe phenotype.[e35] A Class III article examining children with early-onset myopathy with signs of inflammation on muscle biopsy identified heterozygous *LMNA* mutations in 11 of 20 patients.[e53]

Conclusion. In children with suspected CMD, muscle biopsy findings predict the subtype-specific diagnosis for merosinopathy most reliably and can detect the likelihood of dystroglycanopathy in general with the exception of the specific dystroglycanopathy syndromes. The data are insufficient to draw conclusions with regard to collagenopathies. These conclusions are based on 3 Class II[e33,e34,e51] and 3 Class III articles.[e35,e52,e53]

Genetic diagnosis.

Question 2. How often does genetic testing confirm a diagnosis of CMD?

With respect to screening characteristics, 1 study met Class II criteria and 44 studies met Class III criteria. The selected studies included 2 for CMD in general, 13 for collagenopathies, 9 for merosinopathy (including 2 prenatal studies), 16 for dystroglycanopathy (including 7 general studies, 4 focusing on Fukuyama MD, 2 on muscle–eye–brain disease, and 3 on Walker–Warburg syndrome), and 5 for extremely rare CMDs. The selected studies were each assigned a diagnostic rating of Class III or IV, with 2 exceptions: one prenatal merosinopathy study met the criteria for Class II (diagnostic), and one Fukuyama MD study met the criteria for Class I (diagnostic).

One large Class III screening study screened multiple genes across the major CMD categories in 101 patients from Australia. The study included patients with collagenopathy, merosinopathy, and dystroglycanopathy and found genetic confirmation of the diagnosis in ~20% of cases.[e54] Another large Class III study screened 214 patients from the United Kingdom who had been evaluated for possible CMD between 2001 and 2008. Of those, 116 were determined to have CMD, and genetic diagnoses were found in 53 of the 116. The distribution included 19% with collagenopathies, 12% with dystroglycanopathies, and 10% with merosinopathies.[e55]

The Class II collagenopathy screening study examined 49 patients with the clinical diagnosis of Ullrich CMD, Bethlem myopathy, or an intermediate phenotype and found mutations in *COL6A1*, *COL6A2*, and *COL6A3* in all of them.[e56] Among the 12 Class III collagenopathy screening studies, 5 studies with sample sizes greater than 10 were found. In the first Class III study, *COL6A1*, *COL6A2*, and *COL6A3* were screened in 79 patients with Ullrich CMD and Bethlem myopathy, and mutations in 1 of these 3 genes were identified in 62% of patients.[e57] In the second Class III study, 34 patients with CMD with complete or partial collagen deficiency on immunohistochemistry were screened for the 3 collagen VI genes, and mutations were identified in 26 (76%).[e58] The third Class III study, on 14 patients with Bethlem myopathy, found collagen VI mutations in 8 of the 14.[e59] In the fourth Class III study, examining 25 patients with a clinical diagnosis of collagenopathy, 15 patients were found to have collagen VI mutations.[e60] The fifth Class III study used comparative genome hybridization array technology to search for unusual mutations in 14 patients with Ullrich CMD and Bethlem myopathy who did not have collagen VI mutations on Sanger sequencing, and found 1 novel mutation in this manner.[e61] In these 5 studies, heterozygous mutations were most common; homozygous mutations tended to occur in some cases of Ullrich CMD and when complete deficiency of collagen was seen on immunohistochemistry. The other 7 Class III studies all had sample sizes smaller than 10 and generally found high rates of mutation detection,[e62–e68] including 1 that documented large genomic deletions in 2 patients[e62] and another that identified compound heterozygous *COL6A2* mutations in 2 unrelated patients with an autosomal recessive form of Bethlem myopathy.[e63]

Among the 7 Class III screening studies examining genetic diagnosis rates in merosinopathy, the 2 largest studies focused on patients with complete deficiency of merosin in muscle tissue. The first study identified *LAMA2* mutations in 26 of 26 patients[e69] and the second study in 21 of 22 patients.[e70] Most of the patients in these studies had compound heterozygous mutations, whereas a few had homozygous mutations or single heterozygous mutations. The other 5 studies had smaller sample sizes with a variable rate of mutation detection.[e33,e71–e74] Of note, 2 of the smaller studies that included a majority of patients with partial merosin deficiency[e73,e74] showed a lower mutation detection rate overall relative to the larger studies that primarily included patients with complete merosin deficiency.[e69,e70]

Two studies examined the accuracy of prenatal genetic testing in fetuses at risk for merosinopathy. One large, international, multicenter study genetically screened 102 fetuses and found 27 with 2 disease alleles, 52 heterozygous carriers, and 23 with no disease alleles (Class II diagnostic / Class III screening[e75]). Among the 27 fetuses predicted to be affected, 10 had immunohistochemical testing on muscle tissue after the pregnancies were terminated and were confirmed to be affected. No false-positive or false-negative results were found. A smaller Class III screening study screened 1 fetus each from 3 women and predicted 1 affected child, who was confirmed postnatally to have merosinopathy on the basis of genetic testing of blood leukocytes and clinical phenotype.[e76]

Seven Class III screening studies, 3 of which were large studies, examined genetic diagnosis issues in dystroglycanopathies across multiple phenotypes. The first large study screened 81 patients for all 6 known genes (*POMT1*, *POMT2*, *POMGnT1*, *FKTN*, *FKRP*, and *LARGE*) and identified mutations in 53% of those patients.[e77] The second large study screened 92 patients in whom *FKRP* had previously been excluded for the other 5 genes.[e39] In the third large study, 61 patients were screened for *POMT1* and *POMT2* only, and mutations were found in 30%.[e78] The studies determined that mutations in *POMT1* and *POMT2* were the most common overall, whereas *POMGnT1* and *FKRP* were less common. The prevalence of *FKTN* mutations was generally lower outside of Japan, but clusters of *FKTN* mutations were identified in 2 studies outside of Japan, including 1 in Korea.[e31,e39] Among children with dystroglycanopathy, mutations in *LARGE* have been described but are rare. Another study also found a low prevalence of *LARGE* in dystroglycanopathies.[e79] A study of 65 histopathologically confirmed fetal cases of cobblestone lissencephaly found that 66% had mutations in *POMT1*, *POMT2*, *POMGnT1*, *LARGE*, *FKTN*, or *FKRP*.[e80] A cohort of 33 patients with dystroglycanopathy was screened for mutations in *WWP1*, with no mutations identified.[e81]

Among the 4 studies on Fukuyama CMD that met Class III screening criteria, 1 study also met Class I diagnostic criteria. This study screened 18 patients with Fukuyama CMD in Japan and identified mutations in all 18, primarily the common retrotransposal insertion.[e30] The other studies confirmed the high rate of the retrotransposal insertion among affected individuals in Japan, with a lower rate of other mutations in *FKTN*.[e24,e82,e83] The carrier frequency in Japan has been estimated to be 1/88.[e24]

Two Class III screening studies on muscle−eye−brain disease indicate that mutations in *POMGnT1* were associated with a high proportion of cases. One study identified *POMGnT1* mutations in all 26 families examined[e40] and the other in all 8 families tested.[e84]

Three Class III studies addressed the question of genetic diagnosis in Walker−Warburg syndrome. The first study screened 40 families for *POMT1*, *POMT2*, *POMGnT1*, *FKTN*, *FKRP*, and *LARGE* and found mutations in 40%.[e25] The study identified four genes—*POMT1*, *POMT2*, *FKTN*, and *FKRP*—as being associated with Walker−Warburg syndrome. The second study also found that *FKTN* mutations were a cause of some cases of Walker−Warburg syndrome.[e85] Two of the studies found that *POMT1* mutations are less commonly associated with Walker−Warburg syndrome than previously thought.[e25,e86]

Some rare CMDs share features of both CMDs and congenital myopathies. These include *SEPN1*-related myopathy (rigid spine MD/multiminicore disease), integrin α-7 deficiency, lamin-associated CMD, and a CMD with mitochondrial structural abnormalities. Two small Class III studies found associations between *SEPN1* mutations and patients with multiminicore myopathy.[e87,e88] Another Class III study demonstrated that *ITGA7* mutations are a rare cause of CMD.[e89] Two children with dropped head syndrome were found to have *LMNA* mutations.[e90] Another unusual CMD is associated with early-onset muscle wasting, intellectual disabilities, and enlarged mitochondria that accumulate at the periphery of muscle fibers. Fifteen cases of this CMD were found to be associated with mutations in *CHKB*.[e91]

Conclusions (genetic diagnosis).

The mutation detection rate for CMDs in general ranges from 20% to 46% (2 Class III studies).[e54,e55]

In children with collagenopathy (Ullrich CMD or Bethlem myopathy), *COL6A1*, *COL6A2*, and *COL6A3* genetic testing possibly has a high likelihood of detecting causative mutations (1 Class II study,[e56] 5 large Class III studies,[e57−e61] and 7 small Class III screening studies[e62−e68]).

In children with complete merosin deficiency on muscle biopsy, *LAMA2* genetic testing has a high likelihood of detecting causative mutations (2 large Class III studies).[e69,e70] In children with partial merosin deficiency, the likelihood of detecting causative *LAMA2* mutations is less consistent (2 smaller Class III studies).[e73,e74] Prenatal genetic testing is highly accurate (1 Class II diagnostic / Class III screening study[e75] and 1 Class III study[e76]).

Genetic testing can detect causative mutations in many children with dystroglycanopathy in general (7 Class III studies), and detection is estimated to be 30% to 66% in those reports (percentages vary in part because the exact genes and the selected cohort vary from study to

study).[e31,e39,e82–e86] However, it is clear from these data that a high proportion of affected children are not likely to have mutations in any of the known genes. In Fukuyama CMD, *FKTN* mutations are detected in as many as 100% of patients (1 Class I diagnostic / Class III screening study[e30] and 3 Class III screening studies[e24,e82,e83]). In muscle–eye–brain disease, *POMGnT1* mutations may be detected in 100% of patients (2 Class III studies).[e40,e89] In Walker–Warburg syndrome, only 40% of patients have mutations in the known genes (1 large Class III study[e25] and 2 smaller Class III studies[e90,e91]). These studies did not include *ISPD*, *DAG1*, and *DPM3*, genes that have been recently described and may also account for dystroglycanopathy.

Complications.

Question 3. How often do patients with CMD experience cognitive, respiratory, or cardiac complications?

Numerous reports highlight a wide spectrum of complications in children and young adults with CMD. Among the studies, 1 Class III article examined the diagnostic utility of polysomnography, 1 Class II study examined rates of cognitive impairment, 8 Class III studies examined complication frequencies and risk factors, 2 Class IV studies examined structural and developmental brain complications, and 2 Class IV studies examined echocardiographic abnormalities in patients with CMD. See the clinical context section for discussion of further consideration of associated complications, including but not limited to aerodigestive issues (dysfunction of the throat, esophagus, or stomach, or a combination of these, leading to airway, breathing, or swallowing dysfunction, or a combination of these), growth issues, and musculoskeletal complications (e.g., scoliosis and joint contractures).

Structural brain malformations have been identified in children with a variety of CMD subtypes, as described previously in the diagnostic section. However, functional CNS complications have not been as thoroughly documented. The Class II article examined 160 patients with CMD in Italy and found that 92 (58%) had cognitive impairment.[e92] In 1 of the Class III articles, a cohort of Japanese children with Fukuyama CMD was reported to have a high incidence of seizures, findings in many cases supported by EEG abnormalities, during a 10-year observation period.[e83] Another Class III article reported that 2 girls with dystroglycanopathy had epilepsy associated with unusual EEG findings.[e93] In 1 of the Class IV studies, 2 patients with merosinopathy were found to have no correlation between brain MRI abnormalities and cognitive outcomes.[e94] Another Class IV study identified 2 patients with Walker–Warburg syndrome complicated by hydrocephalus and seizures; the hydrocephalus was stabilized by ventriculoperitoneal shunting procedures.[e95]

The current literature does not identify specific diagnostic tools for the development of acute and chronic respiratory complications in children with CMD, although 1 small study examined the utility of polysomnography. One of the Class III studies, which examined 102 patients with CMD, found an overall respiratory complication rate of 12%; however, 13 additional patients

who had died were not included in the analysis, an indicator that the true complication rate may be higher.[e96] In another Class III study, 13 patients with Ullrich CMD found that forced vital capacity (FVC) was < 80% predicted in all patients by age 6 years. An annual average decrement of 2.6% (SD 4.1%) in FVC was reported. Mean age at onset of noninvasive ventilation support was 14.3 years (SD 4.7). Although not focused on treatment, the study also reported that the use of noninvasive ventilation or scoliosis surgery was not associated with improved FVC.[e6] Another Class III study examined the use of polysomnography for the diagnosis of sleep-disordered breathing in 2 patients with CMD and 2 patients with rigid spine syndrome and found that all subjects experienced nocturnal hypoventilation and hypoxemia.[e97]

Cardiac manifestations and complications occur but are not consistent across CMD subtypes. One of the Class III studies previously mentioned noted an overall cardiac complication rate of 6% in a cohort of 102 patients with CMD.[e96] Three Class III studies examined echocardiographic measurements of myocardial and ventricular dimension in children with CMD but did not correlate these findings with clinical symptoms. An estimated 8% to 30% of patients with merosin-positive CMD had significantly depressed cardiac function based on shortening and ejection fraction on echocardiography. Structural or valvular abnormalities were not identified.[e98–e100] The currently available data are not sufficient to study correlations between cardiac complications with age or the clinical course for the various CMD subtypes. One of the Class IV studies, a case series, detected a higher incidence of echocardiographic dysfunction in merosin-negative CMD vs merosin-positive CMD.[e101] Another Class IV series, examining 9 patients with rigid spine syndrome, found that 5 had mitral valvular abnormalities, which have not been identified in other CMD subtypes.[e102]

In a Class III study of 14 children with merosinopathy, the families of all 14 reported that their children had feeding difficulties; the study showed that all but the youngest child (a 2-year-old) had abnormal swallowing on videofluoroscopy.[e103]

Conclusions (complications).

Various CNS, respiratory, and cardiac complications have been identified in children with CMD. There is insufficient evidence to draw comprehensive conclusions as to the risk factors and frequency of these complications in the various subtypes. However, seizures are common in Fukuyama CMD and respiratory complications in Ullrich CMD. These conclusions are based on 1 Class II study,[e92] 9 Class III studies,[e6,e83,e93,e96–e100,e103] and 4 Class IV studies.[e94,e95,e101,e102]

Treatments.

Question 4. Are there effective treatments for complications of CMD, including scoliosis and nutritional deficiencies?

Review of the treatment literature identified no prospective intervention studies for contracture treatment, scoliosis prevention, or nutrition optimization for children and young adults with CMD. A single Class III study of spinal fusion demonstrated correction and prevention of progression of scoliosis and pelvic obliquity over 2 years, resulting in improved or stable balance and sitting posture. The impact on respiratory status and other complications is unclear, as pulmonary function declined after surgical intervention, a finding which may be related to disease progression.[e104]

Conclusions.

Because only 1 Class III study[e104] was identified that specifically addressed this question, the evidence is insufficient to determine whether surgical correction of scoliosis results in stabilization of skeletal abnormalities, sitting, balance, respiratory status, and longer-term outcomes. In general, due to the absence of prospective interventional studies, the evidence is insufficient to support or refute use of specific therapeutic interventions to prevent nutrition-related complications, contractures, or scoliosis.

No data are available to support the use of gastrostomy in children with CMD.

PRACTICE RECOMMENDATIONS

Given the lack of literature directly relevant to CMDs for some of the clinical questions, some of the recommendations below are based in part on evidence from other neuromuscular disorders of childhood.

Section AA. General recommendations.

CMD is a category of rare, complex genetic disorders with multiorgan system complications, and the various subtypes display a wide spectrum of phenotypes (EVID). These patients may develop various combinations of cardiovascular, gastrointestinal/nutritional, neurologic, ophthalmologic, orthopedic, and pulmonary manifestations (EVID). Multidisciplinary teams are recommended in the care of patients with complex neuromuscular conditions such as amyotrophic lateral sclerosis,[e105] and are thus widely believed to be effective in the care of children with complex medical needs such as those with CMD, despite regional variability in the composition and availability of such clinics (RELA). Neuromuscular specialists, particularly child neurologists and physiatrists with subspecialty training, are key members of such teams, as are physicians from other specialties (e.g., cardiology, gastroenterology, neurology, ophthalmology, orthopedic surgery, pulmonology) and allied health professionals with relevant expertise (e.g., dieticians, genetic counselors, nurses, nurse practitioners, occupational therapists, physical therapists, and speech–language pathologists) (PRIN).

Recommendations.

AA1. Physicians caring for children with CMD should consult a pediatric neuromuscular specialist for diagnosis and management (Level B).

AA2. Pediatric neuromuscular specialists should coordinate the multidisciplinary care of patients with CMD when such resources are accessible to interested families (Level B).

AA3. When genetic counselors are available to help families understand genetic test results and make family-planning decisions, physicians caring for patients with CMD might help families access such resources (Level B).

Section A. Use of clinical features, MRI, and muscle biopsy in diagnosis.

Many children and adults with CMD may present with subtle features and milder clinical severity with later onset (EVID). However, patients with some of the classic CMD subtypes, including collagenopathies and dystroglycanopathies, have distinct phenotypic features that may help focus the diagnostic process (EVID). Serum CK levels may be helpful in identifying potential cases (RELA).[e106–e109] Recognition and evaluation of clinical features characteristic of CMD can be difficult in atypical and late-onset cases (PRIN).

Recommendation.

A1. Physicians should use relevant clinical features such as ethnicity and geographic location, patterns of weakness and contractures, the presence or absence of CNS involvement, the timing and severity of other organ involvement, and serum CK levels to guide diagnosis in collagenopathies and in dystroglycanopathies (Level B).

Interpretation of muscle biopsy findings, especially in children, is heavily dependent on technique and the experience of the pathologist or neuromuscular specialist who interprets the studies. Proper interpretation of these studies requires knowledge of the clinical context as well as availability of advanced testing capabilities such as immunohistochemistry and electron microscopy. In the proper setting such as a multidisciplinary neuromuscular clinic with access to sophisticated muscle pathology resources, muscle biopsy is often a valuable component of the diagnostic process and may facilitate genetic diagnosis and genetic counseling. Even in cases where a genetic diagnosis cannot easily be obtained, the knowledge obtained from a muscle biopsy may help families and providers better understand the disease process affecting specific patients (PRIN).

Recommendations.

A2. Physicians might order muscle biopsies that include immunohistochemical staining for relevant proteins in CMD cases for which the subtype-specific diagnosis is not

apparent after initial diagnostic studies, if the risk associated with general anesthesia is determined to be acceptable (Level C).

A3. When muscle biopsies are indicated in suspected CMD cases, they should be performed and interpreted at centers experienced in this test modality. In some cases, optimal diagnostic information may be derived when the biopsy is performed at one center and interpreted at another (Level B).

Typical brain MRI findings of white matter abnormalities in merosinopathies can be found consistently above the age of 6 months,[e77,e110] and the structural brain abnormalities that often accompany the dystroglycanopathies are well documented (EVID). These neuroimaging findings however, may be misinterpreted by adult neuroradiologists or radiologists who are not accustomed to the myelination patterns of infants and toddlers, and by those who are unfamiliar with the patterns observed in patients with rare genetic disorders such as merosinopathies (PRIN).

Muscle ultrasound and MRI studies can help distinguish neurogenic from myopathic disorders[e48] and show pathognomonic patterns for specific CMD subtypes such as Bethlem myopathy (EVID).[e47] Muscle MRI studies likewise can help identify CMD subtypes, including collagenopathies and *SEPN1*-related myopathies (EVID).[e49]

Recommendations.

A4. Physicians should order brain MRI scans to assist with the diagnosis of patients who are clinically suspected of having certain CMD subtypes, such as merosinopathies and dystroglycanopathies, if the potential risk associated with any sedation is determined to be acceptable and if a radiologist or other physician with the appropriate expertise is available to interpret the findings (Level B).

A5. Physicians might order muscle imaging studies of the lower extremities for individuals suspected of having certain CMD subtypes such as collagenopathies (ultrasound or MRI) and *SEPN1*-related myopathy (MRI), if the risk associated with any sedation needed is determined to be acceptable and if a radiologist or other physician with the appropriate expertise is available to interpret the findings (Level C).

Section B: Genetic diagnosis.
Causative genetic mutations have been found in the majority of cases of CMD, and the remainder of cases likely also harbors such genetic mutations (EVID). Targeted genetic testing often identifies causative mutations in the classic CMD subtypes, such as Ullrich CMD, Bethlem myopathy, merosin-deficient CMD, Fukuyama CMD (specifically in Japan), muscle–eye–brain disease, and Walker–Warburg syndrome (EVID). However, the cost of traditional Sanger

sequencing for some of the larger associated genes, such as *COL6A1*, *COL6A2*, *COL6A3*, and *LAMA2*, presents an obstacle to universal application of such sequencing, even though the testing is readily available (RELA).[e111] Genetic diagnoses are beneficial to the patient, as they often enable physicians to provide more accurate prognoses and facilitate genetic counseling and family-planning discussions, and may enable patients to become more aware of future clinical trials for which they may be eligible (PRIN). A substantial proportion of patients with CMD remain without a genetic diagnosis because of lack of access to genetic testing resources in some cases and unidentified causative genes in other cases, although this proportion is expected to decline over time (EVID). Prenatal genetic diagnosis is accurate in fetuses at risk for merosinopathy and is likely to be accurate in other CMD cases in which the familial mutations are known (RELA).[e75,e76] Ethical issues may arise when a family is considering prenatal diagnosis for severe neuromuscular conditions, as has been discussed for Duchenne MD (RELA).[e112]

Recommendation.

> B1. When available and feasible, physicians might order targeted genetic testing for specific CMD subtypes that have well-characterized molecular causes (Level C).

The analysis also indicates that a large number of patients with CMD do not have mutations in one of the currently known genes (EVID). The cost of next-generation sequencing (whole-exome and whole-genome sequencing) is dropping rapidly, to the point where these technologies are now readily available to many researchers who seek novel causative disease genes (RELA).[e15] Several medical centers and commercial genetic-testing companies have begun offering next-generation sequencing on a clinical basis (RELA).[e113] These technologies have the potential, not only of facilitating the identification of novel disease genes, but also of identifying mutations in myopathy genes that were previously associated with different phenotypes (PRIN). This option will become increasingly accessible, accurate, and cost-effective over time, and may largely supplant traditional Sanger sequencing in the future (INFER). The percentage of individuals affected by CMD who have molecular diagnoses is expected to rise steadily over the next decade as next-generation sequencing becomes widely used on a clinical basis (INFER).

Recommendation.

> B2. In individuals with CMD who either do not have a mutation identified in one of the commonly associated genes or have a phenotype whose genetic origins have not been well characterized, physicians might order whole-exome or whole-genome sequencing when those technologies become more accessible and affordable for routine clinical use (Level C).

Section C. Complications and treatment.

Patients with CMD experience a broad spectrum of respiratory, musculoskeletal, cognitive, and cardiac complications with variable tempo between individuals (EVID). This reflects variations

among CMD subtypes and interventions, although the literature review did not identify specific risk or mitigating factors (EVID). In the absence of immediate evidence-based practice, neurologists and other providers may, in appropriate circumstances, extrapolate from early-onset neuromuscular and neuromotor diseases for which consensus guidelines have been developed on the basis of both established principles of care and limited outcomes and intervention trials (RELA).[e114–e118] There are currently no curative CMD subtype-specific interventions (EVID). Thus, all complication screening and interventions are intended to promote growth and potential development, mitigate cumulative morbidities, optimize function, and limit mortality while maximizing quality of life (EVID).[e119]

Recommendations.

C1. At the time of diagnosis, the physician should advise families regarding areas of uncertainty with respect to clinical outcomes and the value of interventions as they pertain to both longevity and quality of life. Physicians should explain the multisystem implications of neuromuscular insufficiency and guide families as they make decisions with regard to the monitoring for and treatment of CMD complications (Level B).

Section D: Respiratory complications.

Patients with respiratory failure from neuromuscular-related weakness may experience conspicuous respiratory symptoms but often do not have symptoms such as dyspnea that precede the onset of respiratory failure (RELA).[e120] Noninvasive and invasive interventions are routinely utilized for children with CMD (PRIN). Pulmonologists, critical care specialists, and respiratory therapists with pediatric training and experience with neuromuscular disorders are most likely to offer treatment options that optimize respiratory outcomes and minimize infection risks and complications (PRIN).

Recommendations.

D1a. Physicians should counsel families of patients with CMD that respiratory insufficiency and associated problems may be inconspicuous at the outset (Level B).

D1b. Physicians should monitor pulmonary function tests such as spirometry and oxygen saturation in the awake and sleep states of patients with CMD, with monitoring levels individualized on the basis of the child's clinical status (Level B).

D2. Physicians should refer children with CMD to pulmonary or aerodigestive care teams, when available, that are experienced in managing the interface between oro-pharyngeal function, gastric reflux and dysmotility, and nutrition and respiratory systems, and can provide anticipatory guidance concerning trajectory, assessment modalities, complications, and potential interventions (Level B).

Section E: Complications from dysphagia.

Patients with neuromuscular disorders often experience dysphagia (impaired swallowing), with implications for growth and nutrition (RELA).[e121] Children with severe neuromuscular conditions, including CMD, may have impaired oro-pharyngeal tone and coordination, placing them at risk for aspiration and potentially limiting the beneficial effects of oral nutrition (EVID, RELA).[e103,e122] Swallowing dysfunction may thus manifest as failure to thrive given nutritional limitations and abnormally high energy expenditures, and may also increase the risk of admission to critical care units and mortality (PRIN). Dysphagia may be diagnosed through standard multidisciplinary evaluations and radiologic studies (PRIN). Safe and adequate nutrition is necessary for optimal health, and thus the potential benefits of improved nutrition with a gastrostomy must be weighed against the potential risks associated with an invasive procedure (PRIN). Some patients may live far from a pediatric referral center, and thus much of their routine care may be coordinated by primary care providers (PRIN).

Recommendations.

E1. Neuromuscular specialists should coordinate with primary care providers to follow nutrition and growth trajectories in patients with CMD (Level B).

E2. For patients with CMD, physicians should order multidisciplinary evaluations with swallow therapists, gastroenterologists, and radiologists if there is evidence of failure to thrive or respiratory symptoms (or both) (Level B).

E3. For patients with CMD, a multidisciplinary care team, taking into account medical and family considerations, should recommend gastrostomy placement with or without fundoplication in the appropriate circumstances (Level B).

Section F: Cardiac complications.

Patients with CMD experience both functional and structural cardiac complications, but the frequency of these for many of the subtypes is unknown.[e101,e102,e123–e127] On the basis of more extensive experience with cardiac complications in Duchenne MD and Becker MD, cardiac involvement may be subclinical and evident only on echocardiography or electrocardiography (or both) in the earlier stages; such involvement may be amenable to pharmacologic therapy (RELA).[e128–e132]

Recommendation.

F1. Physicians should refer children with CMD, regardless of subtype, for a baseline cardiac evaluation. The intervals of further evaluations should depend on the results of the baseline evaluation and the subtype-specific diagnosis (Level B).

Section G: Periprocedural complications.

Patients with neuromuscular diseases are at increased risk for periprocedural complications, including airway problems, suboptimal pain control, pulmonary complications, prolonged recovery times, and complications of bed rest and deconditioning (RELA).[e104,e133–e135]

Recommendations.

> G1. Prior to any surgical interventions and general anesthesia in the setting of CMD, physicians should discuss the potential increased risk of complications with patients' families, as these factors may affect decision making with regard to whether to consent to certain elective procedures (Level B).

> G2. When children with CMD undergo procedures involving sedation or general anesthesia, physicians should monitor longer than usual in the immediate postoperative period to diagnose and treat respiratory, nutritional, mobility, and gastrointestinal mobility complications (Level B).

Section H: Musculoskeletal complications.

Patients with CMD are at increased risk of musculoskeletal complications, including skeletal deformities and contractures (EVID). Range-of-motion exercises are straightforward interventions that generally do not involve significant risk to affected children, but the efficacy of such exercises has not been established in the literature (EVID). Such an exercise program may be a component of physical therapy but may also be performed by the patient and family (INFER). Data on the efficacy of bracing are also lacking for children with CMD (EVID). It is generally accepted that orthopedic surgical interventions such as heel cord–lengthening procedures relieve tendon contractures at least in the short term; however, the long-term efficacy is not clear (PRIN). Neuromuscular blocking agents (e.g., botulinum toxin) can cause prolonged worsening of weakness in patients with neuromuscular diseases (RELA).[e136–e139]

Recommendations.

> H1. Physicians should refer to allied health professionals, including physical, occupational, and speech therapists; seating and mobility specialists; rehabilitation specialists; and orthopedic surgeons, to help maximize function and potentially slow the progression of musculoskeletal complications in children with CMD (Level B).

> H2. Physicians may recommend range-of-motion exercises, orthotic devices, heel cord–lengthening procedures, or a combination of these interventions for children with CMD in certain circumstances (Level B).

H3. Physicians might avoid using neuromuscular blocking agents (e.g., botulinum toxin) in patients with CMD, unless the contractures are determined to cause significantly greater impairment than would any potential worsening of weakness in the targeted muscle groups (Level C).

Section I: Educational adjustments.

Prior to school age, children at risk for developmental delays are eligible for early intervention services as federally mandated. The Individuals with Disabilities Education Improvement Act of 2004 guarantees children with disabilities a free and appropriate public education (PRIN).[e140]

Recommendations.

I1. Physicians should refer children with CMD to special education advocates, developmental specialists, and education specialists when appropriate for individual circumstances (Level B).

RECOMMENDATIONS FOR FUTURE RESEARCH

Despite the advances in genetic knowledge of the CMDs, many patients appear not to have mutations in the known causative genes, an indication that novel CMD genes remain to be discovered. This is especially true for children with Walker–Warburg syndrome or with dystroglycanopathies that do not easily fit in one of the classic phenotypes. Thus, further genetic research is needed.

The clinical presentations of the various CMD subtypes have been well described, and as the genetic knowledge of these diseases becomes more complete, better genotype–phenotype correlations will be made. However, gaps in knowledge remain with regard to the clinical courses of, complications associated with, and optimal treatment regimens for the various subtypes. Standardized outcome measures would also help promote more rigorous research that would help identify complications and optimize treatment in these patients.[e141] Further studies with respect to patient safety and quality improvement would be pertinent to the goal of improving the long-term outcomes for these children.

Thus, the following topics merit further research:

1. Gene discovery in CMD
2. Genotype–phenotype studies in CMDs, especially longitudinal studies
3. Frequency and risk factors for various complications in CMDs
4. The merits of various therapeutic interventions for CMDs

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CONFLICT OF INTEREST

The American Academy of Neurology and American Association of Neuromuscular & Electrodiagnostic Medicine are committed to producing independent, critical, and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN and AANEM keep separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN and AANEM limit the participation of authors with substantial conflicts of interest. The AAN and AANEM forbid commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least three AAN committees, at least one AANEM committee, a network of neurologists, *Neurology* peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com. For complete information on this process, access the 2004 AAN process manual.[e28]

Table e-1. The congenital muscular dystrophies

Disease	Gene symbol	Protein
Collagenopathies: autosomal recessive and autosomal dominant		
Ullrich CMD	*COL6A1*[e65,e142]	Collagen 6α1
	COL6A2[e36,e66]	Collagen 6α2
	COL6A3[e143]	Collagen 6α3
Bethlem myopathy	*COL6A1*[e144]	Collagen 6α1
	COL6A2[e144]	Collagen 6α2
	COL6A3[e145]	Collagen 6α3
Merosinopathy: autosomal recessive		
Merosin-deficient CMD	*LAMA2*[e33]	Merosin
Dystroglycanopathies: autosomal recessive		
Fukuyama CMD	*FKTN*[e24]	Fukutin
Muscle–eye–brain disease	*POMGnT1*[e23,e40,e84]	POMGnT1
	FKRP[e146]	Fukutin-related protein
	POMT2[e38,e147]	POMT2
Walker–Warburg syndrome	*POMT1*[e86,e148]	POMT1
	POMT2[e149]	POMT2
	POMGnT1[e150]	POMGnT1
	FKTN[e85]	Fukutin
	FKRP[e146]	Fukutin-related protein
	LARGE[e79]	LARGE
	ISPD[e17,e151–e153]	ISPD
Primary α-dystroglycanopathy	*DAG1*[e22]	α-dystroglycan
MDDGA8	*POMGnT2/GTDC2*[e16]	POMGnT2
MDDGA10	*TMEM5*[e17]	TMEM
MDDGA11	*B3GALNT2*[e18]	B-1,3-N-acetylgalactosaminyltransferase2
MDDGA12	*SGK196*[e19]	Protein-O-mannose kinase
MDDGA13	*B3GNT1*[e20]	β-1,3-N-acetylglucosaminyltransferase 1

MDDGA14	*GMPPB*[e21]	GDP-mannose pyrophosphorylase B
Unclassified CMDs		
Rigid spine syndrome	*SEPN1*[e10]	Selenoprotein N, 1
	FHL1[e11]	Four-and-a-half LIM domain 1
Multiminicore disease	*SEPN1*[e87]	Selenoprotein N, 1
LMNA-associated CMD	*LMNA*[e12]	Lamin A/C

See MuscleGeneTable.fr for current information.

Abbreviations: CMD = congenital muscular dystrophy; CMDs = congenital muscular dystrophies.

Table e-2. Clinical features of the congenital muscular dystrophies

Disease	Onset	Weakness	Cardiac	Respiratory	CNS	Ocular	
Collagenopathies: autosomal recessive and autosomal dominant							
Ullrich CMD	Birth	++	0	++	0	0	
Bethlem myopathy	Birth	+	+	+	0	0	
Merosinopathy: autosomal recessive							
Merosin-deficient CMD	Birth	++	+	++	+ (white matter lesions; seizures; mild cognitive involvement)	+ (reports of ophthalmoplegia)	
Dystroglycanopathies: autosomal recessive							
Fukuyama CMD	Birth	++	++	++	+ (seizures, cognitive involvement)	+	
Muscle–eye–brain disease	Birth	+++	0	?	++ (seizures, cognitive involvement)	+++	
Walker–Warburg syndrome	Birth	+++	0	?	+++	+++	
Unclassified CMDs							
Rigid spine disease	Birth	++	++	++	?	?	
Multiminicore disease	Birth	++	?	++	?	?	
LMNA-associated CMD	Birth	++	+	++	?	?	

0, none; +, mild; ++, moderate; +++, severe

Abbreviations: CMD = congenital muscular dystrophy; CMDs = congenital muscular dystrophies; CNS = central nervous system.

Appendix e-1. Glossary of terms

Congenital: Traditionally refers to diseases in which clinical manifestations are present at birth, including CMD; however, genetic discoveries suggest that patients with similar phenotypes but slightly later onset may have essentially the same diseases, and thus the term *congenital muscular dystrophy* is now recognized to encompass MDs with onset in the first 2 years of life, especially during infancy (the first year of life).

Founder mutation: Occurs when a population is established by a relatively small number of individuals, with the potential for a specific disease-causing mutation to propagate among a number of families who are not obviously related.

Next-generation sequencing (also known as high-throughput sequencing): Represents the first major advance in DNA sequencing technology since Sanger sequencing (see next) was developed in the 1970s. The key breakthrough was the application of massively parallel sequencing reactions to generate relatively short DNA sequences that could then be matched to the relevant sections of the reference sequence. Variations of next-generation sequencing include targeted sequence capture, whole-exome sequencing, and whole-genome sequencing.

Sanger sequencing: Discovered by Frederick Sanger in the 1970s; made DNA sequencing widely accessible to laboratories and, later, to diagnostic facilities around the world. The fundamental conceptual breakthrough was the use of modified nucleotides to determine the exact sequence of a given DNA strand.

Appendix e-2: Resources for genetic testing

A general resource that is helpful for physicians ordering genetic tests is GeneTests:
GeneTests.org. This website lists facilities that offer testing for specific genes in the
United States and other countries, and provides links to individual test facility websites.

In the United States, clinical testing for many of the genes discussed in this guideline is available
at various facilities, including the following:

- Baylor College of Medicine, Houston, Texas: www.bcm.edu

- Claritas Genomics, Cambridge, Massachusetts: ClaritasGenomics.com

- Emory Genetics Laboratory, Atlanta, Georgia: geneticslab.emory.edu

- Prevention Genetics, Marshfield, Wisconsin: PreventionGenetics.com

- University of Chicago Genetic Services Laboratory, Chicago, Illinois:
DNATesting.UChicago.edu

Genetic testing technology is undergoing rapid changes, and it is likely that much clinical
sequencing of individual genes will be replaced by whole-exome or whole-genome
sequencing (or both) within the next decade. It is not clear yet which facilities will offer
the most accurate testing at the lowest cost.

Appendix e-3: 2013–2015 AAN Guideline Development Subcommittee (GDS) members

Cynthia Harden, MD (Chair); Steven R. Messé, MD, FAAN (Vice-Chair); Richard L. Barbano, MD, PhD, FAAN; Jane Chan, MD, FAAN; Diane Donley, MD; Terry Fife, MD, FAAN; Jeffrey Fletcher, MD; Michael Haboubi, MD; John J. Halperin, MD, FAAN; Cheryl Jaigobin, MD; Andres M. Kanner, MD; Jason Lazarou, MD; David Michelson, MD; Pushpa Narayanaswami, MD, MBBS; Maryam Oskoui, MD; Tamara Pringsheim, MD; Alexander Rae-Grant, MD; Kevin Sheth, MD, FAHA; Kelly Sullivan, PhD; Theresa A. Zesiewicz, MD, FAAN; Jonathan P. Hosey, MD, FAAN (Ex-Officio); Stephen Ashwal, MD, FAAN (Ex-Officio); Deborah Hirtz, MD, FAAN (Ex-Officio); Jacqueline French, MD, FAAN (Ex-Officio)

Appendix e-4: Mission statement of AAN GDS

The mission of the AAN GDS is to prioritize, develop, and publish evidence-based guidelines related to the diagnosis, treatment, and prognosis of neurological disorders.

The AAN GDS is committed to using the most rigorous methods available within our budget, in collaboration with other available AAN resources, to most efficiently accomplish this mission.

Appendix e-5: AANEM Practice Issues Review Panel (PIRP) members

Yuen T. So, MD, PhD (Co-Chair); Williams S. David, MD, PhD (Co-Chair); Paul E. Barkhaus, MD; Earl J. Craig, MD; Prabhu D. Emmady, MD; Kenneth J. Gaines, MD; James F. Howard, MD; Atul T. Patel, MD; Bharathi Swaminathan, MD; Darrell T. Thomas, MD; Gil I. Wolfe, MD

Appendix e-6: Complete search strategy

The complete search strategy is available as an electronic data supplement to this article on the *Neurology*® website. To obtain the search strategy, locate the "appendix e-6 search strategy" pdf at Neurology.org.

Appendix e-7: AAN rules for classification of evidence for risk of bias

For questions related to therapeutic intervention

Class I

- Randomized, controlled clinical trial (RCT) in a representative population
- Masked or objective outcome assessment
- Relevant baseline characteristics are presented and substantially equivalent between treatment
  groups, or there is appropriate statistical adjustment for differences
- Also required:
a. Concealed allocation
b. Primary outcome(s) clearly defined
c. Exclusion/inclusion criteria clearly defined
d. Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the
study) and crossovers with numbers sufficiently low to have minimal potential for bias
e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the
following are also required*:
    1. The authors explicitly state the clinically meaningful difference to be excluded by defining
       the threshold for equivalence or noninferiority
    2. The standard treatment used in the study is substantially similar to that used in previous
       studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of
       administration, dose, and dosage adjustments are similar to those previously shown to be
       effective)
    3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on
       the standard treatment are comparable to those of previous studies establishing efficacy of
       the standard treatment
    4. The interpretation of the study results is based on a per-protocol analysis that accounts for
       dropouts or crossovers

Class II

- Cohort study meeting criteria a–e above or an RCT that lacks one or two criteria b–e

- All relevant baseline characteristics are presented and substantially equivalent among treatment
groups, or there is appropriate statistical adjustment for differences

- Masked or objective outcome assessment

Class III

- Controlled studies (including studies with external controls such as well-defined natural history
controls)

- A description of major confounding differences between treatment groups that could affect
outcome**

- Outcome assessment masked, objective, or performed by someone who is not a member of the treatment team

Class IV

- Did not include patients with the disease

- Did not include patients receiving different interventions

- Undefined or unaccepted interventions or outcome measures

- No measures of effectiveness or statistical precision presented or calculable

*Numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III
**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data)

For questions related to screening (yield)

Class I

- Study of a cohort of patients at risk for the outcome from a defined geographic area (i.e., population based)

- The outcome is objective

- Also required:

a. Inclusion criteria defined

b. At least 80% of patients undergo the screening of interest

Class II
- A non–population-based, nonclinical cohort (e.g., mailing list, volunteer panel) or a general medical, neurology clinic/center without a specialized interest in the outcome. Study meets criteria a and b (see Class I)
- The outcome is objective

Class III

- A referral cohort from a center with a potential specialized interest in the outcome

Class IV

- Did not include persons at risk for the outcome

- Did not statistically sample patients, or patients specifically selected for inclusion by outcome

- Undefined or unaccepted screening procedure or outcome measure

- No measure of frequency or statistical precision calculable

Appendix e-8: Steps and rules for formulating recommendations

Constructing the recommendation and its rationale

> *Rationale for recommendation summarized in the Clinical Context includes three categories of premises:*

- Evidence-based conclusions for the systematic review
- Stipulated axiomatic principles of care
- Strong evidence from related conditions not systematically reviewed

Actionable recommendations include the following mandatory elements:

- The patient population that is the subject of the recommendation

- The person performing the action of the recommendation statement

- The specific action to be performed

- The expected outcome to be attained

Assigning a level of obligation

> *Modal modifiers used to indicate the final level of obligation (LOO)*

- Level A: "Must"

- Level B: "Should"

- Level C: "Might"

- Level U: No recommendation supported

LOO assigned by eliciting panel members' judgments regarding multiple domains, using a modified Delphi process. Goal is to attain consensus after a maximum of three rounds of voting. Consensus is defined by:

- $\geq$ 80% agreement on dichotomous judgments

- $\geq$80% agreement, within one point for ordinal judgments

- If consensus obtained, LOO assigned at the median. If not obtained, LOO assigned at the 10th percentile

Three steps used to assign final LOO:

1. Initial LOO determined by the cogency of the deductive inference supporting the recommendation on the basis of ratings within four domains. Initial LOO anchored to lowest LOO supported by any domain
   - Confidence in evidence. LOO anchored to confidence in evidence determined by modified form of the Grading of Recommendations Assessment, Development and Evaluation process[e154]
     - Level A: High confidence
     - Level B: Moderate confidence
     - Level C: Low confidence
     - Level U: Very low confidence

- Soundness of inference assuming all premises are true. LOO anchored to proportion of panel members convinced of soundness of the inference
  - Level A: 100%
  - Level B: ≥80% to < 100%
  - Level C: ≥50% to <80%
  - Level U or R: <50%
- Acceptance of axiomatic principles: LOO anchored to proportion of panel members who accept principles
  - Level A: 100%
  - Level B: ≥80% to < 100%
  - Level C: ≥50% to <80%
  - Level U or R: <50%
- Belief that evidence cited from rerated conditions is strong: LOO anchored to proportion of panel members who believe the related evidence is strong
  - Level B: ≥80% to 100% (recommendations dependent on inferences from nonsystematically reviewed evidence cannot be anchored to a Level A LOO)
  - Level C: ≥50% to <80%
  - Level U or R: <50%
2. LOO is modified mandatorily on the basis of the judged magnitude of benefit relative to harm expected to be derived from complying with the recommendation
   - Magnitude relative to harm rated on 4-point ordinal scale
     - Large benefit relative to harm: benefit judged large, harm judged none
     - Moderate benefit relative to harm: benefit judged large, harm judged minimal; or benefit judged moderate, harm judged none
     - Small benefit relative to harm: benefit judged large, harm judged moderate; or benefit judged moderate, harm judged minimal; or benefit judged small, harm judged none
     - Benefit to harm judged too close to call: Benefit and harm judged to be equivalent
   - Regardless of cogency of the recommendation the LOO can be no higher than that supported by the rating of the magnitude of benefit relative to harm
     - Level A: Large benefit relative to harm
     - Level B: Moderate benefit relative to harm
     - Level C: Small benefit relative to harm
     - Level U: Too close to call
   - LOO can be increased by one grade if LOO corresponding to benefit relative to harm greater than LOO corresponding to the cogency of the recommendation
3. LOO optionally downgraded on the basis of the following domains
   - Importance of the outcome: critical, important, mildly important, not important
   - Expected variation in patient preferences: none, minimal, moderate, large

- Financial burden relative to benefit expected: none, minimal, moderate, large
- Availability of intervention: universal, usually, sometimes, limited

Appendix e-9: Clinical contextual profiles

Physicians caring for children with CMD should consult a pediatric neuromuscular specialist for diagnosis and management (Level B).

Strength of Recommendation

Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	0	Usually	7	Universal	3	Yes
Financial burden	Prohibitive	0	Moderate	0	Minimal	4	None	6	Yes
Variation in preferences	Large	0	Moderate	0	Small	2	Minimal	8	Yes
Importance of outcomes	Not important	0	Somewhat Imp	2	Very Imp	8	Critical	0	Yes
Benefit relative to Harm	Too Close	0	Modest	0	Moderate	2	Large	8	Yes

Strength of Inference

Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	x	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

Pediatric neuromuscular specialists should coordinate the multidisciplinary care of patients with CMD when such resources are accessible to interested families (Level B).

Strength of Recommendation

Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	0	Usually	8	Universal	2	Yes
Financial burden	Prohibitive	0	Moderate	0	Minimal	5	None	5	Yes
Variation in preferences	Large	0	Moderate	0	Small	2	Minimal	8	Yes
Importance of outcomes	Not important	0	Somewhat Imp	3	Very Imp	7	Critical	0	Yes
Benefit relative to Harm	Too Close	0	Modest	0	Moderate	1	Large	9	Yes

Strength of Inference

Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	x	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

When genetic counselors are available to help families understand genetic test results and make family-planning decisions, physicians caring for patients with CMD might help families access such resources (Level B).

Strength of Recommendation

Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	0	Usually	9	Universal	1	Yes
Financial burden	Prohibitive	0	Moderate	1	Minimal	3	None	6	No
Variation in preferences	Large	0	Moderate	0	Small	2	Minimal	8	Yes
Importance of outcomes	Not important	0	Somewhat Imp	2	Very Imp	8	Critical	0	Yes
Benefit relative to Harm	Too Close	0	Modest	1	Moderate	1	Large	8	No

Strength of Inference

Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

Physicians should use relevant clinical features such as ethnicity and geographic location, patterns of weakness and contractures, the presence or absence of CNS involvement, the timing and severity of other organ involvement, and serum CK levels to guide diagnosis in collagenopathies and in dystroglycanopathies (Level B).

Strength of Recommendation

Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	0	Usually	2	Universal	8	Yes
Financial burden	Prohibitive	0	Moderate	0	Minimal	2	None	8	Yes
Variation in preferences	Large	0	Moderate	0	Small	2	Minimal	8	Yes
Importance of outcomes	Not important	0	Somewhat Imp	1	Very Imp	3	Critical	6	No
Benefit relative to Harm	Too Close	0	Modest	0	Moderate	0	Large	10	Yes

Strength of Inference

Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

Physicians might order muscle biopsies that include immunohistochemical staining for relevant proteins in CMD cases for which the subtype-specific diagnosis is not apparent after initial diagnostic studies, if the risk associated with general anesthesia is determined to be acceptable (Level C).

Strength of Recommendation

Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	1	Usually	8	Universal	1	Yes
Financial burden	Prohibitive	0	Moderate	3	Minimal	5	None	2	No
Variation in preferences	Large	0	Moderate	0	Small	1	Minimal	8	Yes
Importance of outcomes	Not important	0	Somewhat Imp	4	Very Imp	5	Critical	1	No
Benefit relative to Harm	Too Close	0	Modest	0	Moderate	6	Large	4	Yes

Strength of Inference

Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

When muscle biopsies are indicated in suspected CMD cases, they should be performed and interpreted at centers experienced in this test modality. In some cases, optimal diagnostic information may be derived when the biopsy is performed at one center and interpreted at another (Level B).

Strength of Recommendation

Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	0	Usually	8	Universal	2	Yes
Financial burden	Prohibitive	0	Moderate	1	Minimal	5	None	4	No
Variation in preferences	Large	0	Moderate	0	Small	1	Minimal	8	Yes
Importance of outcomes	Not important	0	Somewhat Imp	4	Very Imp	6	Critical	0	Yes
Benefit relative to Harm	Too Close	0	Modest	0	Moderate	3	Large	7	Yes

Strength of Inference

Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

Physicians should order brain MRI scans to assist with the diagnosis of patients who are clinically suspected of having certain CMD subtypes, such as merosinopathies and dystroglycanopathies, if the potential risk associated with any sedation is determined to be acceptable and if a radiologist or other physician with the appropriate expertise is available to interpret the findings (Level B).

Strength of Recommendation

Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	1	Usually	5	Universal	4	No
Financial burden	Prohibitive	0	Moderate	0	Minimal	4	None	6	Yes
Variation in preferences	Large	0	Moderate	0	Small	1	Minimal	8	Yes
Importance of outcomes	Not important	0	Somewhat Imp	0	Very Imp	9	Critical	1	Yes
Benefit relative to Harm	Too Close	0	Modest	1	Moderate	3	Large	6	No

Strength of Inference

Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

Physicians might order muscle imaging studies of the lower extremities for individuals suspected of having certain CMD subtypes such as collagenopathies (ultrasound or MRI) and *SEPN1*-related myopathy (MRI), if the risk of any sedation needed is determined to be acceptable and if a radiologist or other physician with the appropriate expertise is available to interpret the findings (Level C).

Strength of Recommendation

Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	1	Usually	7	Universal	0	Yes
Financial burden	Prohibitive	1	Moderate	2	Minimal	3	None	2	No
Variation in preferences	Large	0	Moderate	0	Small	2	Minimal	6	Yes
Importance of outcomes	Not important	1	Somewhat Imp	5	Very Imp	2	Critical	0	No
Benefit relative to Harm	Too Close	0	Modest	2	Moderate	3	Large	3	No

Strength of Inference

Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	x	No
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

When available and feasible, physicians might order targeted genetic testing for specific CMD subtypes that have well-characterized molecular causes (Level C).

Strength of Recommendation

Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	1	Usually	7	Universal	0	Yes
Financial burden	Prohibitive	0	Moderate	2	Minimal	2	None	4	No
Variation in preferences	Large	0	Moderate	0	Small	2	Minimal	6	Yes
Importance of outcomes	Not important	0	Somewhat Imp	4	Very Imp	3	Critical	1	No
Benefit relative to Harm	Too Close	0	Modest	1	Moderate	0	Large	7	Yes

Strength of Inference

Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	x	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

In individuals with CMD who either do not have a mutation identified in one of the commonly associated genes or have a phenotype whose genetic origins have not been well characterized, physicians might order whole-exome or whole-genome sequencing when those technologies become more accessible and affordable for routine clinical use (Level C).

Strength of Recommendation

Modifier	R/U		C		B		A		Consensus
Availability	Limited	1	Sometimes	4	Usually	3	Universal	0	No
Financial burden	Prohibitive	2	Moderate	3	Minimal	0	None	3	No
Variation in preferences	Large	0	Moderate	0	Small	2	Minimal	6	Yes
Importance of outcomes	Not important	0	Somewhat Imp	6	Very Imp	2	Critical	0	Yes
Benefit relative to Harm	Too Close	0	Modest	1	Moderate	5	Large	2	No

Strength of Inference

Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	x	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

At the time of diagnosis, the physician should advise families regarding areas of uncertainty with respect to clinical outcomes and the value of interventions as they pertain to both longevity and

quality of life. Physicians should explain the multisystem implications of neuromuscular insufficiency and guide families as they make decisions with regard to the monitoring for and treatment of CMD complications (Level B).

Strength of Recommendation

Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	0	Usually	1	Universal	9	Yes
Financial burden	Prohibitive	0	Moderate	0	Minimal	2	None	8	Yes
Variation in preferences	Large	0	Moderate	0	Small	2	Minimal	8	Yes
Importance of outcomes	Not important	0	Somewhat Imp	0	Very Imp	5	Critical	5	Yes
Benefit relative to Harm	Too Close	0	Modest	0	Moderate	2	Large	8	Yes

Strength of Inference

Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

Physicians should counsel families of patients with CMD that respiratory insufficiency and associated problems may be inconspicuous at the outset (Level B).

Strength of Recommendation

Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	0	Usually	1	Universal	9	Yes
Financial burden	Prohibitive	0	Moderate	0	Minimal	2	None	8	Yes
Variation in preferences	Large	0	Moderate	0	Small	2	Minimal	8	Yes
Importance of outcomes	Not important	0	Somewhat Imp	0	Very Imp	4	Critical	6	Yes
Benefit relative to Harm	Too Close	0	Modest	0	Moderate	1	Large	9	Yes

Strength of Inference

Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

Physicians should monitor pulmonary function tests such as spirometry and oxygen saturation in the awake and sleep states of patients with CMD, with monitoring levels individualized on the basis of the child's clinical status (Level B).

Strength of Recommendation

Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	0	Usually	4	Universal	6	Yes
Financial burden	Prohibitive	0	Moderate	1	Minimal	4	None	5	No
Variation in preferences	Large	0	Moderate	0	Small	2	Minimal	8	Yes
Importance of outcomes	Not important	0	Somewhat Imp	1	Very Imp	7	Critical	2	No
Benefit relative to Harm	Too Close	0	Modest	0	Moderate	2	Large	8	Yes

Strength of Inference

Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

Physicians should refer children with CMD to pulmonary or aerodigestive care teams, when available, that are experienced in managing the interface between oro-pharyngeal function, gastric reflux and dysmotility, and nutrition and respiratory systems, and can provide anticipatory guidance concerning trajectory, assessment modalities, complications, and potential interventions (Level B).

Strength of Recommendation

Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	0	Usually	5	Universal	3	Yes
Financial burden	Prohibitive	0	Moderate	3	Minimal	0	None	5	No
Variation in preferences	Large	0	Moderate	0	Small	2	Minimal	6	Yes
Importance of outcomes	Not important	0	Somewhat Imp	3	Very Imp	5	Critical	0	Yes
Benefit relative to Harm	Too Close	0	Modest	0	Moderate	1	Large	7	Yes

Strength of Inference

Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	>50% to < 80%	>80% to < 100%	100%	Yes
Strong related evidence	<50%	>50% to < 80%	>80% to 100%	X	Yes
Acceptance of Principles	<50%	>50% to < 80%	>80% to < 100%	100%	Yes
Logical	<50%	>50% to < 80%	> 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

Neuromuscular specialists should coordinate with primary care providers to follow nutrition and growth trajectories in patients with CMD (Level B).

Strength of Recommendation

Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	0	Usually	0	Universal	8	Yes
Financial burden	Prohibitive	0	Moderate	1	Minimal	2	None	5	No
Variation in preferences	Large	0	Moderate	0	Small	2	Minimal	6	Yes
Importance of outcomes	Not important	0	Somewhat Imp	0	Very Imp	2	Critical	6	Yes
Benefit relative to Harm	Too Close	0	Modest	0	Moderate	1	Large	7	Yes

Strength of Inference

Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	>50% to < 80%	>80% to < 100%	100%	Yes
Strong related evidence	<50%	>50% to < 80%	>80% to 100%	X	Yes
Acceptance of Principles	<50%	>50% to < 80%	>80% to < 100%	100%	Yes
Logical	<50%	>50% to < 80%	> 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

For patients with CMD, physicians should order multidisciplinary evaluations with swallow therapists, gastroenterologists, and radiologists if there is evidence of failure to thrive or respiratory symptoms (or both) (Level B).

Strength of Recommendation

Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	0	Usually	3	Universal	5	Yes
Financial burden	Prohibitive	0	Moderate	1	Minimal	2	None	5	No
Variation in preferences	Large	0	Moderate	0	Small	2	Minimal	6	Yes
Importance of outcomes	Not important	0	Somewhat Imp	1	Very Imp	6	Critical	1	Yes
Benefit relative to Harm	Too Close	0	Modest	0	Moderate	1	Large	7	Yes

Strength of Inference

Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

For patients with CMD, a multidisciplinary care team, taking into account medical and family considerations, should recommend gastrostomy placement with or without fundoplication in the appropriate circumstances (Level B).

Strength of Recommendation

Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	0	Usually	5	Universal	3	Yes
Financial burden	Prohibitive	0	Moderate	2	Minimal	5	None	1	No
Variation in preferences	Large	0	Moderate	0	Small	2	Minimal	6	Yes
Importance of outcomes	Not important	0	Somewhat Imp	1	Very Imp	7	Critical	0	Yes
Benefit relative to Harm	Too Close	0	Modest	1	Moderate	2	Large	5	No

Strength of Inference

Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

Physicians should refer children with CMD, regardless of subtype, for a baseline cardiac evaluation. The intervals of further evaluations should depend on the results of the baseline evaluation and the subtype-specific diagnosis (Level B).

Strength of Recommendation

Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	0	Usually	8	Universal	2	Yes
Financial burden	Prohibitive	0	Moderate	1	Minimal	8	None	1	Yes
Variation in preferences	Large	0	Moderate	0	Small	3	Minimal	7	Yes
Importance of outcomes	Not important	0	Somewhat Imp	0	Very Imp	10	Critical	0	Yes
Benefit relative to Harm	Too Close	0	Modest	1	Moderate	0	Large	9	Yes

Strength of Inference

Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

Prior to any surgical interventions and general anesthesia in the setting of CMD, physicians should discuss the potential increased risk of complications with patients' families, as these factors may affect decision making with regard to whether to consent to certain elective procedures (Level B).

Strength of Recommendation

Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	1	Usually	4	Universal	5	No
Financial burden	Prohibitive	0	Moderate	0	Minimal	1	None	9	Yes
Variation in preferences	Large	0	Moderate	1	Small	4	Minimal	5	No
Importance of outcomes	Not important	0	Somewhat Imp	0	Very Imp	10	Critical	0	Yes
Benefit relative to Harm	Too Close	0	Modest	0	Moderate	2	Large	8	Yes

Strength of Inference

Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	>50% to < 80%	>80% to < 100%	100%	Yes
Strong related evidence	<50%	>50% to < 80%	>80% to 100%	X	Yes
Acceptance of Principles	<50%	>50% to < 80%	>80% to < 100%	100%	Yes
Logical	<50%	>50% to < 80%	> 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

When children with CMD undergo procedures involving sedation or general anesthesia, physicians should monitor longer than usual in the immediate postoperative period to diagnose and treat respiratory, nutritional, mobility, and gastrointestinal mobility complications (Level B).

Strength of Recommendation

Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	1	Usually	7	Universal	2	No
Financial burden	Prohibitive	0	Moderate	0	Minimal	6	None	4	Yes
Variation in preferences	Large	0	Moderate	0	Small	3	Minimal	7	Yes
Importance of outcomes	Not important	0	Somewhat Imp	0	Very Imp	10	Critical	0	Yes
Benefit relative to Harm	Too Close	0	Modest	0	Moderate	1	Large	9	Yes

Strength of Inference

Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	>50% to < 80%	>80% to < 100%	100%	Yes
Strong related evidence	<50%	>50% to < 80%	>80% to 100%	X	Yes
Acceptance of Principles	<50%	>50% to < 80%	>80% to < 100%	100%	Yes
Logical	<50%	>50% to < 80%	> 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

Physicians should refer to allied health professionals, including physical, occupational, and speech therapists; seating and mobility specialists; rehabilitation specialists; and orthopedic surgeons, to help maximize function and potentially slow the progression of musculoskeletal complications in children with CMD (Level B).

Strength of Recommendation

Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	0	Usually	7	Universal	1	Yes
Financial burden	Prohibitive	0	Moderate	0	Minimal	3	None	5	Yes
Variation in preferences	Large	0	Moderate	0	Small	2	Minimal	6	Yes
Importance of outcomes	Not important	0	Somewhat Imp	0	Very Imp	7	Critical	1	Yes
Benefit relative to Harm	Too Close	0	Modest	0	Moderate	1	Large	7	Yes

Strength of Inference

Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

Physicians may recommend range-of-motion exercises, orthotic devices, heel cord–lengthening procedures, or a combination of these interventions for children with CMD in certain circumstances (Level B).

Strength of Recommendation

Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	0	Usually	7	Universal	1	Yes
Financial burden	Prohibitive	1	Moderate	0	Minimal	6	None	1	Yes
Variation in preferences	Large	0	Moderate	0	Small	2	Minimal	6	Yes
Importance of outcomes	Not important	0	Somewhat Imp	1	Very Imp	6	Critical	1	Yes
Benefit relative to Harm	Too Close	0	Modest	1	Moderate	6	Large	1	Yes

Strength of Inference

Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

Physicians might avoid using neuromuscular blocking agents (e.g., botulinum toxin) in patients with CMD, unless the contractures are determined to cause significantly greater impairment than would any potential worsening of weakness in the targeted muscle groups (Level C).

Strength of Recommendation

Modifier	R/U		C		B		A		Consensus
Availability	Limited	1	Sometimes	2	Usually	0	Universal	5	No
Financial burden	Prohibitive	0	Moderate	3	Minimal	3	None	2	No
Variation in preferences	Large	0	Moderate	0	Small	2	Minimal	6	Yes
Importance of outcomes	Not important	0	Somewhat Imp	3	Very Imp	1	Critical	4	No
Benefit relative to Harm	Too Close	2	Modest	0	Moderate	2	Large	4	No

Strength of Inference

Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

Physicians should refer children with CMD to special education advocates, developmental specialists, and education specialists when appropriate for individual circumstances (Level B).

Strength of Recommendation

Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	0	Usually	5	Universal	5	Yes
Financial burden	Prohibitive	0	Moderate	1	Minimal	5	None	4	No
Variation in preferences	Large	0	Moderate	0	Small	2	Minimal	8	Yes
Importance of outcomes	Not important	0	Somewhat Imp	0	Very Imp	10	Critical	0	Yes
Benefit relative to Harm	Too Close	0	Modest	0	Moderate	1	Large	9	Yes

Strength of Inference

Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	$\geq$50% to < 80%	$\geq$80% to < 100%	100%	Yes
Strong related evidence	<50%	$\geq$50% to < 80%	$\geq$80% to 100%	X	Yes
Acceptance of Principles	<50%	$\geq$50% to < 80%	$\geq$80% to < 100%	100%	Yes
Logical	<50%	$\geq$50% to < 80%	$\geq$ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

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